Excipient-API interactions in dry powder inhalers

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Review Article

ABSTRACT

There remains a paucity of predictive models to evaluate the suitability of excipients or excipient mixtures for dry powder inhalers because a large number of interdependent variables affect both formulation and inhaler performance. The problem is compounded by empirical studies that are performed under different experimental conditions which make data comparison difficult. An easily calculable molecular parameter, the Parachor, relates structural constants to surface tension. When applied in conjunction with results obtained from inverse gas chromatography, the Parachor can be used to calculate adhesive and cohesive surface energies between excipients and active pharmaceutical ingredients. Values calculated from the Parachor are consistent with qualitative hypotheses and agree reasonably well with published quantitative results. The ability to both achieve and predict the free particle fraction from Parachor derived surface energy data represents a new paradigm worthy of further perusal.

KEY WORDS: Dry powder inhaler, lactose, excipient, aerosolization, fine particle fraction, adhesive energy, cohesive energy, lung deposition, inverse gas chromatography, cohesive adhesive balance, particle-particle interactions, Parachor

INTRODUCTION

A recent editorial painted a bleak picture regarding the understanding of the relationship between the physicochemical characteristics of the most widely used carrier in adhesive mixtures for dry powder inhalers, lactose, and the performance of those dry powder inhalers. The author cited a list of factors responsible for this situation and recommended areas where further research might prove fruitful in turning information into knowledge (1). To this effect, others (2) have suggested that standard experimental conditions and data reporting criteria be adopted so that a database of results may be constructed to facilitate performance prediction. The urgency of the need for a predictive model is further exemplified when two APIs are used in combination and the ratio of the APIs during co-deposition into the lungs affects efficacy. Particle engineering techniques such as sonocrystallization have emerged, partly in response to a lack of predictive API/ excipient interaction, mixing and aerosolization models (3).

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This review attempts to collate disparate information from the literature into a coherent whole. While recognizing that data generated under different experimental conditions/ methods with different materials may not yield mathematically exquisite correlations, general relationships may still be discernible. Physicochemical data will be examined to ascertain whether qualitative or quantitative predictions relating to the degree of cohesiveness and/or adhesiveness, fine particle fraction (FPF) or aerosol performance can be made *a priori*. To this effect, a new term is introduced, the *Cohesive Index* (CI), that is consistent with bulk surface energy predictions and can be correlated with a fundamental property of molecular structure, the Parachor. Data obtained from single crystal measurements using atomic force microscopy (cohesive-adhesive balance (CAB) of adhesive mixtures) will be compared to those obtained using 'bulk' methods such as inverse gas chromatography (dispersive (γ^{LW}) surface free energy and the electron acceptor (γ^{+}) and electron donor (γ^{-}) components of the polar surface free energy of the individual constituents). In addition, the validity of the 'passivation hypothesis' to explain the benefit of mixing lactose coarse and fine particles on the FPF will be examined based on quantitative surface energy values generated by inverse gas chromatography.

The totality of the information presented in this paper may hence serve as a useful guide in choosing a particular excipient (or a processed excipient whose surface energy has been altered) or a particular mixture of excipients for a particular API to yield a theoretical maximum fine particle (respirable) fraction (FPF). The fact that this paper succeeds in arriving at (admittedly crude) quantitative predictive relationships between readily calculable structural constants and adhesive energy indicates that a more rigorous and exhaustive data mining of the existing literature can lead toward a better understanding of surface and interface chemistry of dry powders. Specific structural parameters such as the Parachor can serve as useful surrogates to estimate surface interactions and analysis (and experiments) along these lines of inquiry seem to be endeavors worthy of pursuit.

Dry powder inhalation formulations are usually composed of micronized drug particles and an excipient carrier. The carrier is instrumental in assuring dosing uniformity during aerosolization and flowability during manufacturing. The design of the formulation must meet contradictory requirements. The adhesive force between drug and carrier particles must be of such a magnitude so as to overcome the drug-drug and excipient-excipient cohesive forces. This is essential to facilitate the uniform dispersion of the drug in the drug-excipient blend and while the powder is being aerosolized. On the other hand the adhesive force between the drug and carrier particles must be weak enough (but not too weak (56)) so that the drug particles can be released from the excipient particles upon aerosolization to form an acceptable FPF. The size of the FPF must be below 5 μm (with a predominantly submicron distribution) to avoid alveolar macrophage uptake (4) and enable penetration deep into the lungs (5), although the dependence of the latter requirement on particle size seems to diminish as the density of the particles decreases (6).

A number of factors determine particle-particle interactions in adhesive mixtures, e.g., surface energy (7), surface morphology (roughness (8), asperity), shape (9), particle size and size distribution (10), order of mixing of ingredients (11), polymorphic form (12), amorphicity (13), humidity (14) and triboelectrification (15). Many of these factors are interdependent, that is, they cannot be varied independently of each other. In addition, the FPF or the respirable fraction is also affected by particle processing history (16) and inhaler design (17).

DISCUSSION

Evidence in the literature generally supports the proposition that the addition of fines to carrier material improves the drug aerosolization and the FPF or respirable dose of cohesive APIs (18). A similar effect is seen with carrier particles that have different mean diameters and similar polydispersity, the FPF increased as the mean diameter decreased (19). Conversely, the removal of fines from carriers decreases drug aerosolization (20) as does an increase in carrier size (21).

At greater drug to carrier ratios (1:36), the delivery device and lactose carrier particle size distribution were found to significantly influence FPF (22). This effect was not significant at lesser drug to carrier ratios (1:400). The FPF was directly proportional to the device air flow rate regardless of the drug to carrier ratio, however the absolute value of FPF increased as the drug to carrier ratio decreased (from 1:1 to 1:8) (23). Another study, performed at drug to carrier ratios between 1:5 and 1:85 found the greatest FPF at a ratio of 1:10, with a decrease at a ratio of 1:5 and progressive decrease at ratios greater than 1:10 (24). The FPF therefore seems to depend in a bell curve manner to the drug loading; decreasing at both low and high loadings and becoming greater at medium loadings.

Another study that investigated the deposition of budesonide from lactose carriers (drug to carrier ratio was 1:100) with different size distributions (broad with lesser mean diameter, narrow with greater mean diameter and a mixture of the two), showed that the FPF was greater for the lactose with the broad size distribution and lesser mean diameter (25). It also showed that the lung deposition of the ^{99m}TC labeled lactose carriers was independent of particle size distribution thus concluding that pulmonary deposition was not a limiting factor for lactose (of different particle size distribution) selection.

Recrystallization of lactose from varying ratios of acetone/water mixtures produced particles that exhibited an increased elongation ratio, decreased mean diameter and a shift from the α to the β polymorph as the acetone proportion in the solvent increased. The FPF of salbutamol sulfate, when mixed with these recrystallized carriers (1: 67.5 ratio), increased >4 times compared with that of the commercial grade lactose (26). A similar effect was observed with mannitol recrystallized form acetone. In this case, both the fine particle fraction and the elongation ratio of the recrystallized mannitol were greater than the commercial grade and produced an increase of FPF when mixed with salbutamol in a 1:67.5 (drug: carrier) ratio (27). The enhancement appears to have an upper limit however, beyond which increasing the elongation ratio does not affect FPF (28).

The guiding principle for formulating powders for DPI seems to be to obtain/prepare a carrier (mixture of lactose fines and lactose coarse particles) and mix the micronized API with this carrier. The hypothesis is that the 'high energy sites' on the coarse particles (29) are occupied or passivated by the fines such that the API particles are forced to adhere to the 'lower energy sites' on the coarse carrier particles (30). The passivation of the high energy sites of the coarse carrier particles can also be performed by utilizing 'force control agents' (31) or FCAs. FCAs may consist of hydrophobic surfactants, polymers (32) or lipids.

The net surface free energy and polydispersity of a blend of fine and coarse particles is greater than that of a carrier consisting only of coarse particles (33). Such a situation has been proposed to lead to an optimal size of the carrier-API agglomerates that are subject to greater de-agglomeration forces in an airstream because these forces are proportional (to an upper limit) to the square (drag force) or cube (collisions) of the diameter of the agglomerate (34). As a result, a greater percentage of API incorporated with the fine/coarse excipient blend may undergo de-agglomeration upon

aerosolization, thereby leading to greater deposition in the deep lung (35).

Using the seminal ideas of Bertholet, who proposed that the interfacial adhesive work between two surfaces is the geometric mean of the cohesive work of the individual surfaces, and that of Fowkes (36), who proposed that intermolecular forces are additive, the Gibbs free energy of adhesion or the work of adhesion between two substances can be expressed in terms of the surface energy components as shown in Equation 1 (37, 38).

$$\Delta G^{a}_{de} = W^{a}_{de} = 2\left[\sqrt{\gamma_d^{LW}\gamma_l^{LW}} + \sqrt{\gamma_e^{LW}\gamma_l^{LW}} - \sqrt{\gamma_d^{LW}\gamma_e^{LW}} - \gamma_l^{LW} - \sqrt{\gamma_d^{+}\gamma_e^{-}} - \sqrt{\gamma_d^{-}\gamma_e^{+}}\right] \quad \text{Eq. 1}$$

Where,

The subscripts d, e and l represent the drug, excipient and the apolar liquid respectively, the first four terms on the right hand side of the equation represent the dispersive or Liftshitz-van der Waals component of the surface free energy and the last two terms represent the specific acid-base component of the surface free energy, further consisting of the electron acceptor (acid) component, γ^{+}, and the electron donor (base) component, γ^{-}.

The apolar solvent used for most of the studies cited in the literature is the propellent 2H, 3H decafluoropentane, the $\gamma_l^{LW}, \gamma_l^{+}$ and γ_l^{-} parameters for this liquid being 13.59, 0 and 0 respectively (39). Adhesive surface free energies are expressed as absolute (positive) values (for ease of interpretation) throughout this report. In addition, where the word "lactose" is not preceded by the word "non-micronized", it represents non-micronized lactose.

Using the technique of inverse gas chromatography (IGC), the acid-base contribution to the non-dispersive component of free energy can be found from alternately probing the adsorbate surface to be studied with acidic and basic polar probe compounds as shown in Equation 2.

$$\Delta G^{AB} = aN_a 2\left\{\left[\gamma_l^{+}\gamma_s^{-}\right]^{1/2} + \left[\gamma_l^{-}\gamma_s^{+}\right]^{1/2}\right\} \quad \text{Eq. 2}$$

Where,

a is the probe molecular cross sectional area, N_a, is Avagadro's number, γ_l^{+} is the electron acceptor (acidic) component of the non-dispersive surface free energy component for the liquid (vapor) probe, γ_l^{-} is the electron donor (basic) component of the non-dispersive surface free energy component of the liquid (vapor) probe, γ_s^{-} is the electron donor (basic) component of the non-dispersive surface free energy of the solid adsorbate and γ_s^{+} is the electron acceptor (acidic) component of the non-dispersive surface free energy of the solid adsorbate. ΔG^{AB} is the acid-base component of the non-dispersive free energy of the solid expressed in KJ/mole.

When basic probe compounds such as tetrahydrofuran, toluene or ethyl acetate are used, $\gamma_l^{+} = 0$ thereby enabling determination of γ_s^{+}. When acidic probe compounds such as chloroform or dichloromethane are used, $\gamma_l^{-} = 0$, thereby enabling determination of γ_s^{-}. The value of γ_s^{+} for mannitol (Table 2) was calculated using 4.7 KJ/mole (40) , 2.9 X 10^{-19} and 20 mJ/m^2 as values for ΔG^{AB}, cross sectional molecular area and γ_l^{-} (for the basic probe, tetrahydrofuran) respectively. Similarly, to calculate the γ_s^{+} for micronized lactose, a ΔG^{AB} value of 5.2 KJ/mol (41) was used using ethyl acetate as the polar probe at 25°C.

Although every attempt was made to compare attributes obtained for similarly processed materials under comparable conditions, in many instances, values for all the three attributes, namely, $\gamma_a^{LW}, \gamma_d^{+}$ and γ_d^{-} were not reported in the same reference manuscript or were not in the same units (42) (e.g. salmeterol). Therefore, some of the values (described above) have been extracted from different manuscripts from the most reported attribute of the specific free energy of adsorption of polar probes. For those drugs where a significant difference between

values calculated from different methods existed in the literature, the values that were most consistent with the structure of the drug were applied. For example, for budesonide, when the cross sectional molecular area and γ_l^- values (43) for the polar basic probe, ethyl acetate, of 3.293 X 10^{-19} m^2 and 19.2 mJ/m^2, were used with the calculated ΔG^{AB} value of 10.52 KJ/mole (44), γ_d^+ was calculated as 36.64 mJ/m^2. γ_d^- was estimated to be 45.8 from the Gutmann (45) $\frac{K_a}{K_b}$ ratio of 0.8 (46). This value of the electron acceptor component of the free energy (as well
as the reported value of 68.47 mJ/m^2 for γ_d^{LW}) appears unduly high compared to similar steroidal drugs.Therefore, γ_d^{LW}, γ_d^+ and γ_d^- of 49.07, 0.34 and 22.47 mJ/m^2 were used as shown in reference 39. Furthermore, particle size distribution data or processing history was often not reported, or was different, when calculated descriptors of γ_d^{LW}, γ_d^+ and γ_d^-, were pooled together from different references.

In Table 1, the attributes of pK_a through melting point were obtained from the open data drug and drug target databases at www.drugbank.ca or at www.chemspider.com.

Values of γ_d^{LW}, γ_d^+ and γ_d^- for micronized (salbutamol, budesonide and formoterol) were taken from reference 39. Values for micronized ipratropium were taken from reference 56. Values for mometasone were taken from reference 57 as were values of γ_d^+ and γ_d^-, for salmeterol. The value of γ_d^{LW} for micronized salmeterol was taken from reference 42.

If either γ^+ or γ^- of the material is < 1, then the material can be classified as being monopolar (47) with either the Lewis acid, or the Lewis base component of the polar surface free energy dominating.

If both γ^+ or γ^- of the material is >1, then the material is bipolar, capable of accepting as well as donating electrons. Monopolar surfaces can interact strongly with other monopolar surfaces of opposite sign (acid-base interactions) and with dipolar surfaces.

Table 1 Physico-chemical characteristics of APIs used in dry powder inhalers

ATTRIBUTE	SALBUTAMOL	BUDESONIDE	MOMETASONE	FLUTICASONE	FORMOTEROL	SALMETEROL	IPRATROPIUM
pKa	14.18	14.91	13.85	14.48	14.21	14.18	NA
H-acceptor	4	6	4	4	5	5.00	2.00
H-donor	4	2	2	1	4	4.00	1.00
Polar surface area (A^2)	72.72	93.06	74.6	80.67	90.82	81.95	46.53
Refractivity	67.87	116.11	110.29	121.65	97.87	122.39	105.90
Polarizability (α_p) ($X10^{24}$)($C/m^2.V$)	28.66	47.11	43.82	48.94	35.56	50.60	37.43
Rotatable bonds	5	4	2	6	8	16.00	6.00
Molar Volume (V_m) (cm^3/mole)	207.6	336.4	379.2	323.16	279.1	379.7	373.7
Water solubility (g/L)	3	0.0457	0.00523	0.0114	0.0416	0.0023	0.0007
Melting point [°C]	157.5	226	219	272	139	75.50	230.00
Parachor $\left[\left(4\sqrt{\frac{mJ}{m^2}}\right)\left(\frac{cm^3}{mol}\right)\right]$	625.2	986.7	1034.1	931.1	829.2	930.3	810.3
Dispersive surface energy, γ_d^{LW} (mJ/m^2)	46.49	49.07	47	47.93*	48.51	45.25	44.90
Electron acceptor component of surface energy, γ_d^+ (mJ/m^2)	8.25	0.34	0.1	Not known	0.11	0.13	26.00
Electron donor component of surface energy, γ_d^- (mJ/m^2)	18.48	22.47	32	Not known	35.04	41.80	8.7

*Calculated from Parachor,, Not known: Not available from the literature, NA Available

Table 2 Physico-chemical characteristics of excipients used or suitable for dry powder inhalers

ATTRIBUTE	LACTOSE MONOHYDRATE	SUCROSE	MANNITOL	ERYTHRITOL	MICRONIZED LACTOSE MONOHYDRATE	TREHALOSE DIHYDRATE
pKa	12.17	12.39	13.38	14.29	12.17	NA
H-acceptor	11	11	6	4	11	11.00
H-donor	8	8	6	4	8	8.00
Polar surface area (A^2)	189.53	189.53	121.38	80.92	189.53	NA
Refractivity	68.34	68.77	38.4	26.48	68.34	NA
Polarizability ($C/m^2.V$)	31.32	31.32	16.82	11.62	31.32	NA
Rotatable bonds	4	5	5	3	4	NA
Water solubility (g/L)	586	824	216	1160	586	689.00
Melting point [°C]	202	185.5	168	NA	202	97.00
Dispersive surface energy, γ_e^{LW} (mJ/m^2)	40.74	43.2	47.9	Not known	42.3	42.90
Electron acceptor component of surface Energy, γ_e^+ (mJ/m^2)	0.15	1.04	9.05	Not known	8.95	5.90
Electron donor component of surface energy, γ_e^- (mJ/m^2)	35.51	51.3	19.9	Not known	29.3	26.10

NA Not Available

According to this definition, salbutamol and ipratropium can be classified as bipolar APIs (the rest being monopolar) while all the excipients are bipolar except for non-micronized lactose monohydrate. For bipolar APIs, the adhesive interactions with the excipients are expected to be greater than for monopolar APIs which is indeed the case (Table 3). This is because the work of adhesion for the former pair also incorporates contributions from the polar component in addition to those from the dispersive component (Keesom, Debye and London interactions).

The values for the drug-excipient adhesive energy (DE) for salbutamol, mometasone, salmeterol and formoterol with the excipients lactose, sucrose and micronized lactose agree to ± 5% (6 pairs), ± 20% (5 pairs) and ± 32% (1 pair) of the values in reference 57. There is a strong positive correlation between the DD cohesive surface energy and γ_d^{LW} (Table 1) with an $R^2 > 0.99$. Weak positive correlations also exists between the polarizability, α_p, and the Parachor, and γ_d^{LW} versus the Parachor per unit molar volume with $R^2 > 0.75$ and $R^2 > 0.65$ respectively. The dispersive energy measured using IGC is usually higher than that obtained with contact angle measurements because the former probes the highest energy sites on the powder surface.

Table 3 Adhesive and Cohesive surface free energies, mJ/m^2

EXCIPIENT	SALBUTAMOL			BUDESONIDE	MOMETASONE	FORMOTEROL	SALMETEROL	IPRATROPIUM	FLUTICASONE (CALCULATED FROM PARACHOR)
	Drug-excipient adhesive energy (DE)	Excipient-Excipient cohesive energy (EE)	Drug-drug cohesive energy (DD)	DE	DE	DE	DE	DE	DE
Lactose	54.45(2.90)	19.88	23.09	28.52(4.13)	25.24(4.29)	26.22(4.28)	25.70(4.16)	79.31(2.36)	26.48(4.23)
Sucrose	67.99(2.69)	21.28	23.09	37.18(3.74)	34.36(3.80)	35.75(3.79)	35.90(3.65)	96.46(2.21)	35.49(3.78)
Mannitol	71.75(2.77)	23.85	23.09	55.19(3.25)	57.36(3.12)	59.78(3.11)	61.78(2.94)	82.74(2.53)	56.90(3.16)
Micronized lactose	74.46(2.54)	20.77	23.09	53.37(3.09)	55.13(2.97)	57.48(2.96)	59.72(2.79)	89.83(2.27)	54.80(3.01)
Trehalose	68.17(2.67)	21.11	23.09	47.99(3.28)	48.86(3.18)	50.92(3.17)	52.50(3.00)	83.69(2.37)	48.82(3.21)

DD: Salbutamol=23.09, Budesonide=24.47, Mometasone=23.37, Formoterol=24.17, Salmeterol=22.42, Ipratropium= 22.22, Fluticasone=23.86 (calculated)
EE: The excipient-excipient cohesive energy values are same regardless of the API, therefore, this column is only presented once in the Table.

However, both IGC and contact angle measurements rank the dispersive component of the free energy of pharmaceutical powders in the same order (48). Therefore, the (relatively) weak correlation between the contact angle dependent attribute, the Parachor and γ_d^{LW} should not affect the rank order of the calculated γ_d^{LW}.

Table 3 shows that, regardless of what excipient they are combined with, ΔG_{de}^{a} (DE), for salbutamol and ipratropium are significantly greater than those for the other APIs, although they are not as pronounced in the case of mannitol and micronized lactose. These APIs also have the least Parachors, which is directly related to their surface tension (and hence is especially suited for use as a surrogate physico-chemical attribute for surface energy related phenomena) via the Macleod-Sugden Equation (49):

$$P = \gamma^{\frac{1}{4}} \frac{M}{(d_1 - d_v)} \qquad \text{Eq.3}$$

Where,

γ is the surface tension, M the molecular weight, d_l and d_v are the densities of the liquid and vapor phase respectively and P is the Parachor. Physico-chemical attributes such as the Hansen solubility parameters (50), molecular orbital indices (51) or multivariate models using molecular descriptors (52) have been used to predict surface properties, but these require more data then the calculation of the Parachor; which can be easily calculated from the structure of the molecule using published group or element contributors.

The Parachors of the APIs were calculated from the group contributions presented in reference 49 and assumed to be substantially additive. The values were found to be accurate within ± 5% when calculated and checked against published values for structurally similar steroids (53). A compound with a smaller Parachor possesses weaker intermolecular forces and is expected to adhere with (relatively) greater force to excipients. When the Parachor is divided by the molar volume, it can be expressed in similar units as those of the surface free energy. The Parachor per unit volume (obtained by dividing P by V_m) is positively correlated to the DD cohesive surface energy, R^2=0.655.

The numbers in brackets in the DE columns of Table 3, termed the *Cohesive Index*, represent a measure of how cohesive the two ingredients (excipient and drug) are, relative to their adhesion to each other. The CI is calculated using Equation 4.

$$CI = \sqrt{\frac{(DD)(EE)}{(DE)}} \qquad \text{Eq. 4}$$

Where,

DD, EE and DE are the attributes in Table 3. CI has a unit of $\sqrt{\frac{mJ}{m^2}}$.

This term is hence formally analogous to the cohesive-adhesive balance (54) (CAB), with the exception that it cannot classify the net force as being either adhesive or cohesive (as CAB can). Instead, the CI represents a gradation of magnitude, the greater the CI, the greater the cohesiveness of the components of the mixture and vice-versa. The CI generally follows the rank order of drug-excipient adhesive surface energy (DE), however, it is easier to interpret than raw DE data because, being a ratio, it is normalized for different APIs across different excipients. For example, a mixture of mometasone and micronized lactose (CI=2.97) is expected to be much more adhesive than a mixture of budesonide and mannitol (CI=3.55). Furthermore, all the APIs adhere more strongly to micronized lactose (CI range=2.31-3.39) than to non-micronized lactose (CI range=2.37-4.28).

Table 4 shows the CAB ratios obtained from Jones *et.al.* (55) compared with the CI values calculated as described above. For budesonide, there is no correlation between the two, the adhesive energy interaction between drug and excipient (DE) decreasing in the order lactose < trehalose < mannitol when measured by the 'bulk' IGC method (CI) while the adhesive energy between drug and excipient decreases in the order mannitol < trehalose < lactose when measured by AFM (CAB). There is, similarly, no correlation between the CI and CAB for formoterol. The pattern for drug-adhesive interaction is similar for salmeterol when measured by AFM or IGC. It has been pointed out that the separation energy measured using AFM and the surface free energy using IGC differ by 5 to 8 orders of magnitude. Therefore, drug to carrier interaction forces are not predictive of surface energy differences (30). While an interesting academic technique, measuring the CAB with AFM does not seem to be representative of practical situations encountered with the mixing of bulk drugs and/or excipients.

Table 4 Correlation between Cohesive index and Cohesive-adhesive balance

	BUDESONIDE		FORMOTEROL		SALMETEROL	
	CI	CAB	CI	CAB	CI	CAB
Lactose	4.13	0.82	4.28	1.16	4.16	2.39
Mannitol	3.25	1.12	3.11	1.18	2.94	0.65
Trehalose	3.28	1.07	3.17	1.02	3.00	1.37

Predictions made using the CAB have not generally been replicated, and in some cases are contradictory to, observations using IGC which more closely mimic situations in industrial scale mixing and size reduction operations.

Cline and Dalby (56) found a direct proportionality between the surface energy interaction between drug and excipient and the FPF as a percent of emitted dose. The FPF increased as the drug-carrier interaction became stronger. Contrary to James *et.al.* (57) who reported an order of magnitude increase in γ^+ when α-lactose monohydrate was (sub)-micronized, these investigators did not find any significant difference in K^A values for grades of lactose that differed in their specific surface areas by an order of magnitude. They hence attributed the increase of performance of the DPI to the requirement that a minimum surface energy interaction between drug and carrier particles was necessary to separate the highly cohesive, micronized drug particles during the blending process and while the powder was being aerosolized.

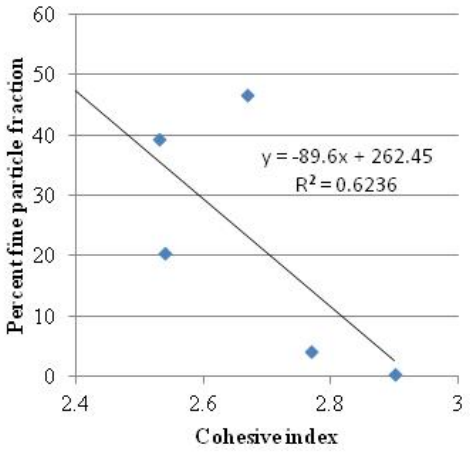

Figure 1 Cohesive index as a predictor of percentage fine particle fraction of emitted dose (FPF values from Table II of reference 56, CI calculated from this paper)

Assuming that any (adhesive) upper limit on the reduction of agglomerates to fine particles can be overcome by inhaler design, Table 3 shows that the adhesive mixtures that will form the greatest FPF are those of iprartopium with lactose, sucrose, micronized lactose and trehalose (CI<2.41). Conversely, adhesive mixtures of budesonide, mometasone, formoterol and salmeterol with lactose will form the least FPF (CI>4.0). A plot of CI versus FPF (FPF values obtained from reference 34) indicates possible correlation, shown in Figure 1, and supports the hypothesis that a minimum adhesive surface free energy is required between drug and carrier (within the confines of current inhaler design) to achieve an acceptable FPF.

Surface energy data has been criticized as being difficult to interpret because it is dependent on testing conditions and does not vary considerably among different batches. It must be remembered that micronized or particle size reduced mixtures of API and carrier are thermodynamically unstable systems that are kinetically stabilized. Knowledge of surface energy is critical in designing optimal aerosol yielding formulations whose surface free energy is as less removed from the stable thermodynamic state as possible, yet can still be aerosolized into an acceptable FPF within inhaler design limitations.

It is surprising that the 'passivation hypothesis' that explains the benefit of mixing coarse and fine lactose powders has not been subjected to empirical testing. This widely disseminated and oft-referenced hypothesis posits that 'high energy' sites on the coarse lactose particles are 'occupied' by fine lactose particles. This, in turn, forces the API particles to occupy only the 'low energy' sites on the coarse lactose particles leading to drug-excipient adhesive forces that can be overcome by aerosolization and fine API particles can be generated for deep lung delivery.

By treating non-micronized and micronized lactose as a drug and excipient, the adhesive energy between the two can be calculated using Equation 1. Table 5 presents the adhesive energy between API and lactose/micronized lactose as well as the adhesive energy between lactose/micronized lactose.

Table 5 Optimization of mixture blend using adhesive surface energy interaction data

API	LACTOSE	MICRONIZED LACTOSE
	Adhesive surface energy, mJ/m^2	
Salbutamol	54.45	74.46
Budesonide	28.52	53.37
Mometasone	25.24	55.13
Fluticasone	29.1 (calculated)	54.96 (calculated)
Formoterol	26.22	57.48
Salmeterol	25.70	59.72
Ipratropium	78.89	86.60
Lactose		53.41

Table 5 shows that the energy required to break interparticle bonds between lactose and micronized lactose is 53.41 mJ/m^2. The energy required to separate the most cohesive drug, budesonide, is 24.47 mJ/m^2. Several situations during the mixing process can be considered:

1. The lactose and micronized lactose are mixed together with an energy input of > 53.41 mJ/m^2 during the mixing process thereby yielding an adhesive mixture of the two ingredients. This is then followed by either step 2, or step 3.

2. The API is then added and the contents mixed with an energy input of > 24.47 mJ/m^2 but less than 53.41 mJ/m^2. These mixing parameters will yield a mixture that closely resembles the one in the 'passivation hypothesis', with the API particle adhering to non-micronized lactose and the adhesion between the non-micronized and micronized lactose remaining unperturbed.

3. The API is then added and the contents mixed with an energy input >53.41 mJ/m^2. In this situation, the adhesion between the non-micronized and micronized lactose is disrupted. API will hence predominantly adhere to the micronized lactose component of the excipient mixture because the adhesive energy between the APIs presented here and micronized lactose is greater than that between the API and lactose. If inhaler design is incapable of generating energy sufficient to break these highly adhesive DE agglomerates, a higher energy input during mixing may decrease the FPF of the aerosolized formulation (58).

The example outlined above emphasizes the importance of the order of mixing (59) and the magnitude of the energy input during mixing processes for DPI formulations. These can significantly impact product performance. Additionally, IGC data for the individual excipient/API batches as well as particle and size distribution characterization are extremely important in designing mixing unit operations.

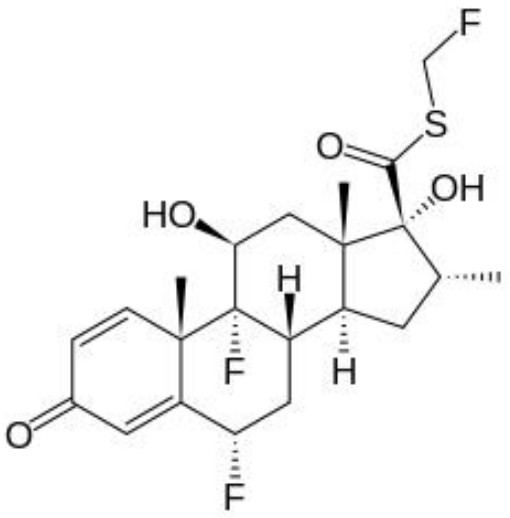

Figure 2 Molecular structure of fluticasone

This simple concept can partly explain why conflicting data exist in the literature with regard to FPF and a variety of surface and non-surface (60) energy attributes for mixed DPI powders.

Estimation of cohesive index, drug-drug cohesive energy (DD) and drug-excipient cohesive energy (DE) for fluticasone

The Parachor value for fluticasone, based on the structure of the molecule (Figure 2), was calculated to be 931.1 $\left(\sqrt[4]{\frac{mJ}{m^2}}\right)\frac{cm^3}{mol}$.

The γ_d^{LW} for fluticasone was obtained by first using the line of best fit for the (P/V_m) and the γ_d^{LW} values for the APIs, then using the line of best fit for the γ_d^{LW} and DD values to obtain the DD for fluticasone. The γ_d^{LW} and DD for fluticasone were calculated to be 47.93 mJ/m^2 and 23.86 mJ/m^2 respectively.

For each excipient, linearised functions were generated by plotting the $\left[\frac{Parachor}{molar\ volume}\right]$ normalized DD surface free energies on the abscissa versus the $\left[\frac{Parachor}{molarvolume}\right]$ normalized DE surface free energies on the ordinate axis for the four monopolar APIs, budesonide, mometasone, formoterol and salmeterol. Good correlation was obtained for all the excipients ($R^2 > 0.84$) except for lactose, where the correlation coefficient was 0.77. Substituting the value of the calculated DD for fluticasone in the equation for each excipient yielded a function wherein the value of DE could be calculated. These values are presented in Table 3. The CI was then calculated from Equation 4.

CONCLUSIONS

Surface energy calculations from inverse gas chromatography can yield valuable information about how a particular API or excipient will behave with respect to cohesive and adhesive forces. While still simplistic in approach, the advantage of such easily calculable data is that it provides a starting point to not only design experiments, but also to logically interpret (apparently) inconsistent results from those experiments. Using the data from four APIs presented in this paper, the unknown cohesive and adhesive energy for a similar (monopolar) compound can be estimated by calculating the surface tension (and hence surface energy) dependent parameter, the Parachor.

The proportion of API that adheres to fine or to coarse particles of the carrier seems to be determined as much by the order of mixing and the energy input during the mixing process, as it does by the physico-chemical characteristics of the fine/coarse carrier blend itself. Surface energy estimations described in this report demonstrate that the energy input during mixing may determine the API adhesion propensity toward different particle size fractions of the excipient/carrier blend. Methods to quantify the energy input during mixing processes should be developed and reported so that FPF data may be contextually interpreted (61). Additionally, the energy input must include the dimensionality of Time because the adhesion energy of particles to a substrate surface increases with the force with which the particles are pressed against the surface (press-on force) (62). Time dependent,

repeated application of the same force has the same effect as increasing the press-on force.

Salbutamol has been disproportionately used as a representative API in published papers. Since salbutamol exhibits the greatest drug-excipient adhesive energies (after ipratropium) with mixtures of micronized and non-micronized lactose monohydrate (the most commonly used excipient blend in DPI), the adhesive forces in a mixture of salbutamol and lactose will be greater than those with other APIs in combination with lactose. Therefore, phenomena of separation or segregation of ingredients over shelf life and dose non-uniformity will be lesser with salbutamol-lactose mixtures. In addition, depending on the magnitude of the CI and the design of the inhaler, FCAs will be lesser able to influence (improve) the FPF of the dispensed aerosol. If conclusions from such experiments are generalized, the attributes of separation of the drug-carrier mixture over shelf life, dose non-uniformity as well as the importance of FCAs to increase performance post-aerosolization will be perceived to be less important in designing DPI formulations. To alleviate this skewed perception, it is recommended that, whenever possible, experiments be performed using APIs that represent both the upper and lower limit of API-excipient interactions in terms of surface energetics, i.e. both monopolar and dipolar APIs be included.

The large number of variables that affect particle-particle interactions, and their interdependence, stymies cause-and-effect conclusions and encourages the execution of more empirical studies, in the hope of eventually accumulating unequivocal evidence of causality (and hence prediction). Regardless of suggestions to the contrary (63), it is useful to attempt generalizations based on what (inconclusive) data exists, so that a particular direction and strategy for future research may either become evident or be discarded. The quantification of surface energetics using an easily calculable molecular structural constant as a tool for prediction of DPI behavior represents such an attempt. It is hoped that this model may be further developed such that the ultimate objective of prediction may be achieved.

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